UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

August 9, 1999

MEMORANDUM

SUBJECT: **Trichlorfon**; Chemical No. 057901. The HED Toxicology Chapter for the Risk Assessment for the Reregistration Eligibility Decision Document (RED), Case # 0104. DP Barcode: D258023.

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Attached is the Toxicology Chapter for trichlorfon, for purposes of issuing a Reregistration Eligibility Decision (RED) Document.

HAZARD CHARACTERIZATION

Hazard Profile

Trichlorfon is an organophosphate insecticide used for the control of household , agricultural, and farm animal insect pests. It is an inhibitor of cholinesterase and produces neurotoxic effects in animals. The toxicological data base for trichlorfon is complete and will support reregistration eligibility (See Table 1).

Following acute, subchronic and chronic exposures the most sensitive indicator of trichlorfon toxicity was cholinesterase inhibition . The acute clinical signs of trichlorfon toxicity are typical of organophosphates and include vomiting, diarrhea, nausea and blurred vision . In a single dose human clinical trial on Alzheimer's patients, the NOAEL and LOAEL for ChE inhibition in plasma and red blood cells was 2.5 and 5.0 mg/kg, respectively. In an acute neurotoxicity study in rats the NOAEL for ChE inhibition (plasma, RBC and brain ChE) was 10 mg/kg. In a three month feeding study in dogs, the NOAEL and LOAEL for ChE inhibition was 0.5 and 2.5 mg/kg/day, respectively. In a ten year chronic feeding/oncogenicity study in Rhesus monkeys, the NOAEL was 0.2 mg/kg/day based on the inhibition of brain ChE activity at 1.0 mg/kg/day (LOAEL).

Trichlorofon was evaluated for carcinogenicity in mice, rats and monkeys. The Health Effects Division (HED) Cancer Assessment Review Committee (CARC) classified trichlorfon as **'not likely to be carcinogenic to humans at low doses, but is likely to be carcinogenic at high doses'.**

Trichlorfon was evaluated for organphosphorus induced delayed neuropathy in chickens. In a 90-day study in hens, there were no overt indications of a response characteristic of delayed neurotoxicity, but there was a slight axonal degeneration at 18 mg/kg/day dose with a NOAEL of 9 mg/kg/day. Tricholrfon induced neurotoxicity was also evaluated in rats following acute or 90-day exposures. Changes in functional Observation Battery (FOB) and motor activity parameters occurred at or above levels causing cholinesterase inhibition.

Trichlorfon causes developmental toxicity in rabbits and rats at or above doses causing maternal toxicity. Similarly offspring toxicity was noted at doses higher than those causing parental toxicity.

Various *in vitro* and *in vivo* mutagenicity tests indicate a mutagenic potential for trichlorfon.

Trihlorfon is rapidly absorbed from the digestive tract and eliminated following metabolism within 24 hours in experimental rats. According to a 1992 International Program on Chemical Safety (IPCS) Environmental Health Criteria Publication on Trichlorfon, it is stated that Trichlorfon metabolizes to form dichlorvos via dehydrochlorination. The main metabolites of trichlorfon found in mammals were

demethyl trichlorfon, demethyl dichlorvos, dimethyl hydrogen phosphate, methyl hydrogen phosphate and phosphoric acid. The main degradation routes of trichlorfon are demethylation, P-C bond cleavage and ester hydrolysis.

TABLE 1: TOXICITY PROFILE OF TRICHLORFON TECHNICAL.

Guideline No.	Study Type	MRID No.	Required	Satisfied
870.1100	Acute Oral Toxicity-Rat	00256446	Yes	Yes
870.1200	Acute Dermal Toxicity-Rat	00090786	Yes	Yes
870.1300	Acute Inhalation Toxicity-Rat	00256446	Yes	Yes
870.2400	Acute Eye Irritation-Rabbit	41571302	Yes	Yes
870.2500	Acute Dermal Irritation-Rabbit	40306901	Yes	Yes
870.2600	Dermal Sensitization-Guinea Pig	00257599	Yes	Yes
870.3200	21-Day Dermal Toxicity-Rabbit	00403069	Yes	Yes
870.6200	Acute Neurotoxicity-Rat	44578001	Yes	Yes
870.6200	Subchronic Oral Neurotoxicity-Rat	43871701	Yes	Yes
870.6100	Acute Delayed Neurotoxicity- Hen	00256446	Yes	Yes
870.6100	90-Day Delayed Neurotoxicity-Hen	40351201 40879301	Yes	Yes
870.4300	Chronic Feeding/ Carcinogenicity-Monkeys	40776001	No	Yes
870.3465	21-Day Inhalation-Rat	00256446	Yes	Yes
870.3150	Subchronic Toxicity/Dog	HED # 1668 & 1669	Yes	Yes
870.4100	Chronic Toxicity/Dog	00090786	Yes	Yes
870.4200	Carcinogenicity/Mice	40782401 40844301	Yes	Yes
870.4300	Combined Chronic Toxicity/ Carcinogenicity/Rat	41056201 41973001	Yes	Yes
870.3700	Developmental Toxicity/Rat	40255601	Yes	No
870.3700	Developmental Toxicity/Rabbit	41565201	Yes	Yes

870.3800	2-Generation Reproduction-Rat	42228301	Yes	Yes
870.5500	Salmonella typhimurium gene mutation	00249535	Yes	Yes
870.5575	Sacharomyces cerevisiae gene mutation	00256446	Yes	Yes
870.5500	Salmonella and E. coli gene mutation	00028625	Yes	Yes
870.5300	in vitro cytogenic study in mammalian cells	00028625	Yes	Yes
870.5550	Unscheduled DNA synthesis in rat hepatocytes	00028625	Yes	Yes
870.5500	Bacterial cells gene mutation	00028625	Yes	Yes
870.5500	Bacterial cells gene mutation	00028625	Yes	Yes
870.5900	Sister Chromatid exchange	40277201	Yes	Yes
870.5900	sister chromatid exchange in Chinese hamster ovary cells	00028625	Yes	Yes
	Clastogenicity in human lymphocytes	40984701?		
870.5500	Bacterial DNA damage/repair	00256446	Yes	Yes
870.7485	Metabolism Study- Rat	40438101	Yes	No

a. Acute Toxicity

Acute toxicity values for tricholrfon in experimental animals as well as Toxicity Categories are summarized in Table 2.

b. Subchronic Toxicity

In a 21-day dermal toxicity study, trichlorfon was administered dermally to rabbits for 15 days (5 days a week for 3 weeks) at doses of 0, 100, 300 or 1000 mg/kg/day. The systemic NOEL was greater than the highest dose tested. The NOAEL for RBC cholinesterase inhibition was 100 mg/kg/day and the LOAEL for cholinesterase inhibition was 300 mg/kg/day based on significant inhibition in RBC cholinesterase activity. (**GLN 870.3200**, MRID# 40306901).

In a 21-day inhalation study, SPF Wistar II strain rats were exposed to trichlorfon levels of 12.7, 35.4 or 103.5 mg/m^3 for 6 hours/day /5 days/week/3 weeks. The NOAEL was 12.7 mg/m^3 and the LOAEL was 35.4 mg/m^3 based on the inhibition of plasma, red blood cell and brain cholinesterase activity. (**GLN 870.3465**, MRID# 00256446).

In a 3-month feeding study dogs receiving dietary doses of 20, 100, 300 or 500 ppm of trichlorfon, the NOAEL was 20 ppm (0.5 mg/kg/day) and the LOAEL was 100 ppm (2.5 mg/kg/day)based on the inhibition of plasma and RBC cholinesterase activity. Brain ChE was not measured. (**GLN 870.3150**, MRID# Not available, HED # 001668 & 001669).

Table 2: ACUTE TOXICITY VALUES AND CATEGORIES OF TRICHLORFON

Guideline Number and Study	MRID #	RESULT	CATEGORY
870.1100 Acute Oral Toxicity - Rat	00256446	LD50=136 - 173 mg/kg	II
870.1200 Acute Dermal Toxicity - Rabbit	00090786	LD50 $ 2 g/kg	III
870.1300 Acute Inhalation Toxicity - Rat	00256446	LC50=533 mg/m^3 - 4 hours	III
870.2400 Acute Eye Irritation - Rabbit	44471301	moderately irritating	II
870.2500 Acute Dermal Irritation - Rabbit	40306901	non irritating	IV
870.2600 Skin Sensitization Guinea Pig	00257599	Moderate contact allergen	NA

c. Neurotoxicity

In acute and subchronic studies, trichlorfon induced inhibition of choliesterase activity and produced alterations in functional obsrvation battery (FOB) parameters. These studies are discussed below.

In an acute neurotoxicity study, Fischer 344 rats received a single oral administration of trichlorfon at 0, 10, 50, or 200 mg/kg. Assessments were made for Functional Observation Battery (FOB) and motor activity; and cholinesterase (plasma, RBC, and brain) activity was measured at same intervals. The NOAEL was 10 mg/kg and the LOAEL was 50 mg/kg based on clinical signs (oral stains, red nasal stains, and urine stains), alterations in FOB, decreased motor activity, and significant plasma, red blood cell, and brain cholinesterase inhibition at 50 mg/kg/day the LOAEL (MRID# 4457801).

A single dose human clinical trial reported in an FAO/WHO monograph (Becker *et al.*, 1990) evaluated the use of trichlorfon in the treatment of Alzheimer's disease. A single oral dose of 0, 2.5, 5.0, 7.5, or 15 mg/kg/day was administered to humans. The NOAEL was 2.5 mg/kg/day and the LOAEL was 5.0 mg/kg/day based on the inhibition of plasma and RBC ChE levels and clinical signs of vomiting, nausea, and diarrhea.

In a 90-day neurotoxicity study in hens, trichlorfon was administered at dose levels of 0, 3, 9 or 18 mg/kg/day. There were no overt indications of a response characteristic of delayed neurotoxicity; however, histologically, a slight effect on nervous tissue, characterized as axonal degeneration was present in hens receiving 18 mg/kg/day. Based on this finding, the NOAEL for neurotoxicity was 9 mg/kg/day. (**GLN 870.6100**, MRID# 0040351201 and 408793-01)

In a subchronic oral neurotoxicity study, groups of Fischer 344 rats were administered nominal concentrations of 0, 100, 500, and 2500 ppm of trichlorfon technical in the diet for 3 months. These concentrations resulted in average daily intake values of 0, 6, 31, and 165 mg/kg/day for males and 0, 7, 35, and 189 mg/kg/day for females. The LOAEL for CHE inhibition (brain, plasma, and RBC) is 500 ppm (31 mg/kg/day). The NOAEL for ChE inhibition is 100 ppm (6 mg/kg/day). The systemic and neurotoxic NOAEL was 31 mg/kg/day and the LOAEL was 165 mg/kg/day based on clinical signs in males and females during the functional observation battery (FOB), a slightly uncoordinated righting reflex in males, reduced motor and locomotor activity in males and females, and minimal myelin degeneration of the spinal nerve roots of males and females.. (**GLN 870.6200**, MRID# 43871701).

d. Chronic Toxicity

A ten year chronic toxicity/carcinogenicity study was conducted in Rhesus monkeys. Trichlorfon was administered via Tang orange drink at doses of 0, 0.2, 1.0 or 5.0 mg/kg/day for six days a week during the ten year testing period. At the levels tested, the compound did not induce any increases in tumor incidence over controls nor were there any pre-neoplastic lesions reported that could be associated with the administration of trichlorfon. The LOAEL was 0.2 mg/kg/day based on findings of decreased plasma (39% decrease in females, no decrease in males), red blood cells (30% decrease in males, no change in females) and brain (22% decrease inmales, no change in females) cholinesterase activity levels. At the highest dose tested (5.0 mg/kg/day), there was a decrease in body weight for both sexes (6 to 33%) and anemia as characterized by decreases in erythrocyte, hemoglobin and hematocrit values. At this same dose level, transitory signs of cholinesterase inhibition were observed in females during the first month of the study. These consisted of pupillary constriction, muscle fasciculation and diarrhea. (**GLN 870.4100 and 870.4200**, MRID# 40776001)

Trichlorfon was tested in male and female beagles at dietary doses of 0, 50, 250, 500 or 1,000 ppm (equivalent to 0, 1.2, 6.3, 12.5 or 25 mg/kg/day). There were no reported adverse

effects on survival or on body weights nor were there any reports of clinical signs that could be associated with trichlorfon administration. Gross findings included mild to moderate enlargement of the spleen at the highest dose tested. Microscopic analysis showed marked congestion of the spleen and lymphoid atrophy of this organ in high dose animals of both sexes. Microscopic findings in the liver of high dose animals consisted of foci of inflammatory cells. The NOAEL in this study was 6.3 mg/kg/day and the LOAEL was 12.5 mg/kg/day based on decreases in serum and RBC ChE activity. This study was classified as supplementary. (**GLN 870.4100**, MRID# 090786). The data requirement for a chronic non-rodent study was satisfied by the ten year monkey study. (**GLN 870.4100**, MRID# 40776001)

e. Carcinogenicity

In a chronic toxicity and carcinogenicity study, trichlorfon was administered to Fischer 344 rats at dietary doses of 0, 100, 300 or 1750 ppm (equivalent to 0, 4.4, 13.3 and 75 mg/kg/day for males; 0, 5.8, 17.4 and 93.7 mg/kg/day for females, respectively) for 24 months. The chronic toxicity NOAEL was 4.4 mg/kg/day and the LOAEL was 13.3 mg/kg/day based on decreases in RBC (17%) and brain (18%) ChE levels and a statistically significant increase in the incidence of renal calcification in males. At the highest dose tested, gross findings included granular kidneys and foci in the lungs of females; and, thickened enlarged duodenum and thickened and granular non-glandular stomachs in males. The gross findings were correlated with microscopic findings of hyperplasia of the small intestines, non-glandular gastritis in the stomach, inflammation of the lung, chronic nephropathy, and renal calcification. Decreases in body weight gain were reported in high dose animals at week 13 (10% in males, 18% in females). In addition, anemia characterized by statistically significant decreases in the hematocrit, hemoglobin, red blood cell counts, and mean corpuscle volume was seen in both sexes. Hypercholesterolemia was also present in the high dose males and females and in the mid-dose males. Under the conditions of the study, the test material was associated with an increase in the incidence of benign pheochromocytomas in high dose males which was slightly outside of the historical control range. **Since these tumors are very common in this strain of rats and were not present in the same strain at a higher dose level in another study (discussed below), they were not considered to be compound related by the HED Carcinogenicity Peer Review Committee (CPRC)** . A statistically significant increase in the incidence of mononuclear cell leukemia was reported for low and high dose males; however, the incidence of this tumor was within the historical control range. The highest dose tested was considered by the CARC as adequate based on the compound-related effects on clinical chemistry parameters, gross and microscopic pathology and clinical findings of paleness and hunched backs in males and rough hair coats in females. (**GLN 870.4100 and 870.4200**, MRID# 41056201).

In an additional 2-year study conducted in Fischer 344 rats at dietary dose levels of 0 or 2500 ppm (equivalent to 0 or 129 mg/kg/day in males and 0 or 159 mg/kg/day in females,

respectively), trichlorfon was associated with an increase in the incidence of alveolar/bronchiolar adenomas in males, renal tubular adenomas in males and alveolar/bronchiolar carcinomas in females. While none of these tumors were reported at statistically significant levels, the incidences were well outside of the historical control range. There was no compound related increase in the incidence of either benign pheochromocytomas or in the incidence of mononuclear cell leukemia.
In this same study, administration of the test material was associated with a decrease in body weight and body weight gain (10.5% males and 18.5 % females), increased incidences of urine stain, rough coats and pale eyes, decreases in erythrocyte parameters (hematocrit, hemoglobin , RBC count and MCV), hypercholesterolemia and increases in hepatic enzymes (SAP, AST, ALT and GGT). Decreases in plasma (63% males, 52% females) and erythrocyte (38% males, 30% females) cholinesterase activity were reported in both sexes of animals when treated groups were compared to controls. Brain cholinesterase activity was 58 and 54% lower than controls for males and females, respectively. **Compound related non-neoplastic lesions included duodenal hyperplasia, gastritis, pulmonary hyperplasia and inflammation, nasolacrimal inflammation, hepatocellular hyperplasia and vacuolation, chronic nephropathy and an increased incidence of dermal lesions were all reported at 2500 ppm.** CPRC concluded that this study was conducted at a level which exceeded the MTD. (**GLN 870.4100 and 870.4200**, MRID# 41973001, 42510301)

In a twenty four-month chronic/carcinogenicity study in CD-1 mice, trichlorfon was administered at dietary dose levels of 0, 300, 900 or 2700 ppm (equivalent to 0, 45, 135 or 405 mg/kg/day, respectively). Clinical signs of toxicity were observed at all dose levels and included vaginal discharges, urine staining and ear lesions. Depressed plasma (57% males, 74% females at HDT), brain (66% males, 71% females) and erythrocyte (35% males, 38% females) cholinesterase levels were reported in all treated animals. A NOAEL for systemic toxicity was not demonstrated in this study. There was a significant trend for increased mortality in female mice. In the low dose females, there was a statistically significant increase in the incidence of alveolar/bronchiolar adenomas and combined alveolar/bronchiolar adenomas and carcinomas. In the mid-dose group, there was a statistically significant increase in the incidence of alveolar/bronchiolar carcinomas and combined alveolar/bronchiolar adenomas and carcinomas. No significant differences were reported at the highest dose tested for lung adenomas, carcinomas or combined tumors. **In males, there was an increase in the incidence of hepatocellular adenomas at all dosed groups; however, the increase was not statistically significant. Based on the clinical signs of toxicity and the effects on ChE activity, it was determined by the HED Cancer Assessment Review Committee (CARC) that trichlorfon was tested at adequate dose levels.** (**GLN 870.4200**, MRID# 40782401, 40844301)

e. Developmental Toxicity

Developmental effects by trichlorfon in rabbits and rats occurred at the same dose levels that caused inhibition of ChE activity in maternal animals.

In a developmental toxicity study in rabbits, trichlorfon was administered by gavage to pregnant does on gestation days 6 thru 18. The doses were 0, 10, 35 or 110 mg/kg/day. The NOAEL and LOAEL for maternal toxicity (ChE inhibition of brain 38% and RBC 20% and abortion) were 10 and 35 mg/kg/day, respectively. The NOAEL and LOAEL for developmental toxicity (an increase in the number of does with resorptions, decreased fetal body weights in males and delayed ossification, primarily in the first sternebrae) were 35 and 110 mg/kg/day, respectively. (**GLN 870.3700**, MRID# 41565201)

In a developmental toxicity study in rats, trichlorfon was administered in the diet at dose levels of 0, 500, 1,125 or 2,500 ppm (equivalent to 0, 45, 102 or 227 mg/kg/day, respectively) from days 6 thru 15 of gestation. The NOAEL for developmental and maternal toxicity were less than 45 mg/kg/day based on decreases in ChE activity (levels not provided) in mothers and reduced ossification of skulls, vertebrae and sternebrae in fetuses. The study was classified unacceptable due to deficiencies in litter and historical control data (**GLN 870.3700**, MRID# 40255601. 41303201, 41303202)

g. Reproductive Toxicity

Trichlorfon did not cause reproductive effects in rats but produced decreased body weights and dilated renal pelvises in pups.

In a two-generation reproduction study conducted in Sprague Dawley rats, trichlorfon was administered at doses of 0, 150, 500 or 1,750 ppm (equivalent to 0, 15, 50 or 175 mg/kg/day, respectively). Parental toxicity was observed at the lowest dose tested and was based on decreases in plasma ChE in F_0 animals (24% lower than controls) and brain cholinesterase activity in both generations (12% for F_0 and 14% for F_1 when compared to controls). In the F_o generation, females had chronic pneumonia and in the F_1 generation, pulmonary and renal lesions were present in high dose animals of both sexes. The pulmonary lesions consisted of chronic pneumonia characterized by thickened alveolar septa, macrophage accumulation, cholesterol clefts, pneumocyte hyperplasia and neutrophilic infiltration. Renal lesions consisted of mineralization and hydronephrosis. The parental LOAEL and NOAEL were 15 mg/kg/day and <15 mg/kg/day, respectively. The LOAEL for offspring toxicity was 175 mg/kg/day based on the presence of dilated renal pelvises and decreased weight of F_1 pups on days 7 and 21. The NOAEL for offspring toxicity is 50 mg/kg/day. No reproductive effects were observed. Therefore, the NOAEL was 175 mg/kg/day. (**GLN 870.3800**, MRID# 422283-01)

g. Mutagenicity

Trichlorfon was mutagenic in both eukaryotic and prokaryotic cell systems as discussed below.

In gene mutation assay with Salmonella typhimurium, trichlorfon was found to be weakly mutagenic at toxic concentrations with or without activation (**GLN 870.5100**, MRID 249535).

In a gene mutation assay conducted with S. cerevisiae, trichlorfon was not mutagenic at levels up to 10,000 µg/ml, in either the presence or absence of activation (**GLN 870.5100**, MRID 256446).

In another gene mutation assay, with Salmonella and E. coli, trichlorfon was tested at doses from 1 µg to 10,000 µg/plate. Trichlorfon induced reversions in Salmonella at doses greater than 5 mg and in E. coli at doses greater than 1 mg/plate. (**GLN 870.5000** , MRID# 00028625)

In an in vitro cytogenetic study in mammalian cells, trichlorfon, at doses ranging from 1 to 145 µg/ml, induced significant increases in mutation frequencies both with and without activation. (**GLN 870.5300**, MRID# 000256446, HED doc. # 004509).

In an unscheduled DNA synthesis study, trichlorfon induced unscheduled DNA synthesis in Wi-38 cells in the absence of S-9 activation (concentration from 0.1 to 10 mg/ml) but not with such activation. (**GLN 870.5550** , MRID# 00028625, HED doc. # 003267). In another test, trichlorfon failed to in induce UDS in rat hepatocytes up to levels of severe toxicity. (**GLN 870.5550 Series**, MRID# 00256446, HED doc. # 004509).

Trichlorfon (doses not stated) was positive for DNA damage and repair in S. typhimurium, but was negative in relative toxicity assays with E. coli and B. subtilis strains. (**GLN 870.5100** , MRID# 00028625, HED doc. # 003267).

In a DNA damage and repair study conducted with S. cerevisiae, trichlorfon was positive for mitotic recombination in the presence and absence of S-9 activation at concentrations from 10 to 50 mg/mL. (**GLN 870.5500**, MRID# 00028625)

At cytotoxic levels of 1,000 µg/ml, trichlorfon was associated with a marginal but significant increase in sister chromatid exchange in Chinese hamster ovary cells. (**GLN 870.5900**, HED doc.# 003267).

Trichlorfon induced sister chromatid exchange at 50 and 100 µg/ml in a dose dependent manner, but results were inconclusive in the presence of S-9 activation (**GLN 870.5900**, MRID # 40277201, HED 006745).

Trichlorfon was clastogenic in human lymphocytes in the absence of S9 activation at doses of 3, 10 or 30 µg/ml. (HED Doc. # 008481).

In a recombinant DNA study conducted at doses of 3, 30 or 300 mg, trichlorfon did not inhibit the growth of Bacillus subtilis. (**GLN 870.5500**, MRID# 00256446)

h. Metabolism

A metabolism study was conducted in rats using four treatment regimes (single dose of 0.2 mg/kg in water by gavage; single dose of 20 mg/kg in water by gavage; ten gavage doses of 0.2 mg/kg in water followed by the radiolabelled compound in water at a dose of 0.2 mg/kg; and single intravenous dose of 0.2 mg/kg into the tail vein). The data collected from the four regimes demonstrated that 80-90% of the test material was excreted within 24 hours. The major route of excretion was via the urine, followed by feces and expired air. One to 2% of the dose was found in the tissues after 96 hours. In this study, the metabolites were not adequately characterized. This study was classified as supplementary, but information was reported which could be used for regulatory purposes. (**GLN 870.7485**, MRID# 40438101)

Trichlorfon metabolizes to form dichlorvos via dehydrochlorination (IPCS, 1992). The main metabolites of trichlorfon found in mammals were demethyl trichlorfon, demethyl dichlorvos, dimethyl hydrogen phosphate, methyl hydrogen phosphate and phosphoric acid. The main degradation routes of trichlorfon are demethylation, P-C bond cleavage and ester hydrolysis.

i. Dermal Absorption

No dermal absorption studies are available.

Reference Dose

The Health Effects Division RfD/Peer Review Committee met on January 13, 1994 and concluded, based on the available data, that trichlorfon was not associated with any significant reproductive and/or developmental toxicity. A chronic RfD of 0.002 mg/kg/day was established based on the results of a ten year chronic feeding study in monkeys in which the LOAEL was 0.2 mg/kg/day (Refer to Chronic toxicity Section above). An uncertainty factor of 100 was used to account for inter-species extrapolation and intra-species variability. The Committee recommended review of trichlorfon by the CPRC.

Other Toxicological Endpoints for Risk Assessment

On February 11, 1999, the Health Effect Division's (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the toxicology database for trichlorfon and selected doses and toxicology endpoints for risk uncertainty factors and margins of exposures for dietary and non-dietary risk assessments assessment, based solely on **animal toxicity studies**. **The February HIARC report supersedes all other reports (RfD, TES, HIARC, etc) for trichlorfon.** (HED Doc. No. 013435). Table 3 provides a summary of Toxicology Endpoint Selection based on this report.

Table 3. The doses and toxicological endpoints selected and Margins of Exposures for various exposure scenarios

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY	MOE[a]
Acute Dietary	NOAEL=10 UF = 100	Clinical signs, plasma, RBC and brain cholinesterase inhibition	Acute Neurotoxicity-Rat Study	Not Relevant
	Acute RfD =0.1 mg/kg/day			
Chronic Dietary	NOAEL=0.2 UF= 100	Brain cholinesterase inhibition in both sexes	Chronic Toxicity-Monkeys	Not Relevant
	Chronic RfD =0.002 mg/kg/day			
Dermal Absorption	Estimated at 10% based upon the comparisons of LOAELs in the oral developmental toxicity (35 mg/kg/day) and the 21-day dermal toxicity (300 mg/kg/day) in rabbits.			
Short-Term (Dermal)	Dermal NOAEL=100	Red blood cell cholinesterase inhibition	21 Day Dermal - Rabbit	100
Intermediate-Term (Dermal)	Dermal NOAEL=100	Red blood cell cholinesterase inhibition	21 Day Dermal - Rabbit	100
Long-Term (Dermal)[b]	Oral NOAEL=0.2	Brain cholinesterase inhibition in both sexes	Chronic Toxicity-Monkeys	100

Inhalation (Any Time Period)	Inhalation NOAEL= 0.0127 mg/L	Plasma, red blood cell, and brain cholinesterase inhibition	21-Day Inhalation-Rat	100

[a]MOEs are for occupational exposure risk assessments. For residential scenarios, target MOE's are lower by a factor of 10 (FQPA).

[b] = Since an oral value was selected, a 10% dermal absorption factor should be used for route to route extrapolation

On August 31, 1994 the CPRC determined that based on the evidence presented, trichlorfon was equivocal for animal carcinogenicity. In a carcinogenicity study in Fisher 344 rats, there was an increase in the incidence of renal tubular adenomas and alveolar/bronchiolar adenomas in males and an increase in the incidence of alveolar/bronchiolar carcinomas in females receiving 2500 ppm of trichlorfon when these groups were compared to concurrent controls. The Committee determined trichlorfon was administered at a dose which exceeded the MTD in this study. The HED Carcinogenicity Peer Review Committee classified trichlorfon a Group E, evidence of non-carcinogenicity for humans.

On February 17, 1999, the Cancer Assessment Review Committee (CARC) evaluated additional data submitted by the registrant on the mammary gland tumors since the 1995 meeting. The CARC concluded that administration of trichlorfon was associated with increasing significant trends for mammary gland adenocarcinomas, adenoacanthomas, and combined adenomas, adenocarcinomas, and adenoacanthomas in female CD-1 mice. There was also a significant difference in the pair-wise comparison of the high-dose group with controls for mammary gland combined adenomas, adenocarcinomas, and adenoacanthomas. Additionally, the incidence was outside the historical control range. However, the highest dose was considered excessive because of significant cholinesterase inhibition and increased mortality. Also, the increase in tumor incidence was seen only at the high-dose level, there was no dose response, no decrease in latency, and there were no precursor changes. Additionally, the CARC concurred with the previous CPRC assessment of the rat and the other mouse tumor data.

The Committee classified Trichlorfon as **"not likely to be carcinogenic to humans at low doses, but is likely to be carcinogenic at high doses"**.

Other Toxicological Considerations

The published literature indicates that a trichlofon preparation known as Metrifonate is used in the treatment of Alzheimer disease and parasites in humans such as cutaneous cysticercosis, urinary schistosomiasis, onchocerciasis. A therapeutic dose of 10 mg/kg given for 2-6 days over few weeks has been reported to be effective in controlling parasitic infestations in schoolchildren with minimal side effects. Metrifonate has been advocated for the treatment of Alzheimer disease at daily doses in excess of 1 mg/kg.

3.2 FQPA Considerations

The FQPA Safety Factor Committee met on June 15 and 16, 1998 to evaluate hazard and exposure data for trichlorfon and recommend application of the FQPA Safety Factor (as required by Food Quality Protection Act of August 3, 1996), to ensure the protection of infants and children from exposure to trichlorfon. The FQPA Safety Factor Committee has determined that the 10x FQPA safety factor is retained for the protection of infants and children from acute and chronic dietary exposure to trichlorfon..

Data gaps include a prenatal developmental toxicity study in rats. A series of publications (listed at the end of this chapter) on the effects of trichlorfon on prenatal brain development in the guinea pig and pigs add more concern regarding its safety in humans (HIARC, August, 1999). **Due to these concerns HIARC is asking for a developmental neurotoxicity study in rats.** The requirement for a prenatal developmental study in guinea pigs is put on reserve pending the results of the developmental neurotoxicity study in rats.

Over 40 literature citations concerning the use of trichlorfon to treat human parasitic infectins and Alzheimer's disease are included at the end of this chapter. Time does not permit their full evaluation.

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